REMARKS

I. Introduction

In response to the Office Action dated April 23, 2003, claims 15 and 21 have been cancelled, claims 16, 19, 20 and 22 have been amended, and 33-35 have been added. Claims 16-20, 22-26 and 33-35 remain in the application. Re-examination and re-consideration of the application, as amended, is requested.

II. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and were not required to distinguish the claims over the prior art. The amendments to the claims introduce no new matter and are fully supported by the specification as filed. Aqueous solutions comprising a pharmaceutically acceptable carrier are discussed throughout the specification, for example at paragraphs 31, 43 and 51.

III. Examiner Interview Summary

Record is made of a telephone interview on July 16, 2003 between Applicants' attorney William Wood and Examiner Dell Chism in connection with the present patent application.

Applicants' Attorney wishes to thank Examiner Chism for his very helpful suggestions regarding clarifying language for the claims.

IV. Non-Art Rejections

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

On page (2) of the Office Action, claims 15-26 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. After a very helpful discussion with Examiner Chism, Applicants have cancelled claims 15 and 21 and added new claims 33 and 34 to address these rejections.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

In paragraphs (5)-(6) of the Office Action, claims 15-16, 20-22, and 26 were rejected under 35 U.S.C. §112, first paragraph. In this rejection the Examiner asserts that the specification, while being enabling for methods of making compositions comprising human insulin/LISPRO heterodimeric complexes, does not reasonably provide enablement for methods of making any/or all compositions comprising a heterodimeric complex of human insulin and any insulin variant. Applicants respectfully traverse the rejection for the reasons noted below.

The instant invention is based on Applicants' discovery that a mixture of two insulin species can form heterodimeric complexes that are more stable than the homodimeric complexes formed by the individual insulin species. The specification teaches human insulin/LISPRO heterodimeric complexes as a working example of the invention and further sets forth methods for assessing the stability of heterodimeric complexes formed by any combination of insulin species.

In the outstanding Office Action, the Examiner asserts that the requirements of 35 U.S.C. §112, first paragraph are not satisfied because the effort needed to make and use the claimed invention constitutes undue experimentation. In particular, the Examiner asserts that "[g]iven the lack of teachings of predictability or unpredictability in the art regarding the variability in the stability of just any human insulin/insulin variant composition and in the absence of sufficient disclosure in applicant's specification to overcome the lack of teachings of predictability and/or unpredictability in the art, it would require undue experimentation by one of skill in the art to be able to make and use the invention commensurate in scope with the claims other than those drawn to human insulin/LISPRO heterodimeric complexes." While Applicants respect the Examiner's concerns about predictability, they nonetheless traverse this rejection in view of their detailed description of assays for assessing the stability of heterodimeric complexes formed by any combination of insulin species (i.e. the Thioflavin-T assays disclosed in Example 2). The disclosure of these assays makes the analysis of any insulin heterodimers routine. Therefore the unpredictability noted by the Examiner does not preclude enablement. In the following paragraph, Applicants use the analogy of a coin toss to illustrate their position.

While outcome of a coin toss is totally unpredictable, one merely needs to observe the tossed coin in order to determine the outcome of heads or tails. In determining whether methods

involving the determination of unpredictable events such as the result of a coin toss satisfy the requirements of 35 USC 112, the focus is not on the unpredictability of the coin toss itself, but rather the effort it takes to determine the outcome and thus make and use the invention commensurate in scope with the claims. In particular, courts state that the very term "experimentation" implies that the success of the particular activity is uncertain (*In re Angstadt and Griffin*, 190 USPQ 215, 219 (CCPA 1976)). Therefore, an analysis under 35 U.S.C. section 112 properly focuses on whether an Applicants' disclosure teaches artisans how to address unpredictable events without undue experimentation so that they can make and use the invention commensurate in scope with the claims.

Applicants' specification provides detailed teachings of how to analyze the presence of stabilizing heterodimeric complexes in any insulin formulations. These procedures are routine experimental protocols that do not constitute undue experimentation. Specifically, in order to determine whether a particular combination of insulin species can be used to generate the stabilized heterodimers of the invention, an artisan only needs to prepare 3 test samples consisting of: (1) the first insulin species alone, (2) the second insulin species alone and (3) a combination of the first insulin species and the second insulin species; and then test the stability of the 3 test samples in an assay such as the Thioflavin-T assays disclosed in Example 2. This disclosure therefore allows an artisan to readily assess the ability of any one insulin species to form a stable heterodimer with another insulin species (e.g. by the routine preparation and testing of the three insulin species formulations as discussed above). While the outcome of a given assay may be unpredictable (like the toss of a coin), the amount of experimentation necessary to determine the result (i.e. prepare and analyze 3 test samples) is not undue. Moreover, this experimentation allows one to make and use the invention as broadly as it is claimed. Consequently, Applicants' disclosure satisfies the requirements of 35 U.S.C. section 112, first paragraph.

Finally, Applicants respectfully point out that once the existence of stable insulin heterodimers are taught in combination with methods for how to assess the stability of any heterodimeric complexes, an artisan can use this disclosure to easily examine formulations comprising mixtures of any two insulin species. Therefore, Applicants' disclosure enables more than just the working human insulin/LISPRO embodiments that are expressly disclosed in the specification. Consequently, Applicants request the allowance of claims that are commensurate with the disclosure they are placing into the public domain.

For these reasons, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

V. Prior Art Rejections

In paragraph (7) of the Office Action, claims 15 and 21 were rejected under 35 U.S.C. §102(b) as being anticipated by Hansen et al., U.S. Patent No. 5,149,777 (Hansen) or Balschmidt et al., EP 0 837 072 A2 (Balschmidt).

In order to constitute an anticipatory reference, the reference must disclose every element recited in the claim. The independent claims are directed to methods for using two different insulin species to make stabilized insulin heterodimer compositions. In this context, the methods recited in the claims include the step of selecting the first and second insulin species so that the heterodimer formed by the first insulin species and the second insulin species is more stable than a homodimer formed by the first insulin species or a homodimer formed by the second insulin species.

Applicants respectfully traverse the Examiner's rejection under 35 U.S.C. § 102(b) because neither Hansen nor Balschmidt teach nor suggest methods that involve the selection of two insulin species to form a heterodimer that is more stable than the respective homodimers. While Hansen teaches insulin preparations containing at least one insulin analog and Balschmidt suggests mixtures of insulin analogues, these references provide no disclosure relating to insulin heterodimers, much less heterodimers selected to be more stable than homodimers formed by the individual insulin species. Consequently, these references cannot teach or suggest the methods for making the heterodimers recited in the claims. For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 102(b).

VI. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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